Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Nevirapine (NVP, Viramune) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Oral Suspension: 10 mg/mL

Tablets: Immediate-release 200 mg tablets; extended-release (XR) 100 mg and 400 mg tablets

Generic Formulations:

- 10 mg/ml suspension
- Immediate-release 200 mg tablets
- XR 400 mg tablets

The oral suspension formulation of brand-name nevirapine (Viramune) is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order it from the Boehringer-Ingleheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Note: Nevirapine (NVP) is often used to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Child and Adolescent Dose:

- In most situations, NVP is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.[a]

Immediate-Release Tablets and Oral Suspension

Gestational Age of 34 to 37 Weeks:

- NVP 4 mg/kg per dose twice daily for the first week, increasing to NVP 6 mg/kg per dose twice daily thereafter (no lead-in dosing).[a]
- This is an **investigational dose** that is not approved by the Food and Drug Administration (FDA).

Gestational Age of ≥37 Weeks to Age of <1 Month:

- NVP 6 mg/kg per dose twice daily (no lead-in dosing).[a]
- This is an **investigational dose** that is not approved by the FDA.
- See Special Considerations for Dosing: Neonates and Premature Infants below.

Aged ≥1 Month to <8 Years:

- NVP 200 mg per m^2 of body surface area per dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate NVP without lead-in dosing (maximum dose of immediate-release tablets is NVP 200 mg twice daily).

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis[b]
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- Shake the oral suspension well before administering and store at room temperature.
- NVP can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14 day lead-in period, do not increase the dose until rash resolves (see Major Toxicities below).
- Extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement below).
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities below).

Aged ≥8 Years:

- NVP 120 mg to 150 mg per m^2 of body surface area per dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is NVP 200 mg twice daily).
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose can be left static to achieve the appropriate mg-per-m^2 dose as the child grows, as long as there are no adverse effects (AEs).

Extended-Release Tablets

Aged ≥6 Years:

- Patients aged ≥6 years who are already taking immediate-release NVP tablets twice daily can be switched to extended-release NVP tablets without lead-in dosing.[a]

Body Surface Area Dosing for Extended-Release Nevirapine Tablets

Body Surface Area	Once-Daily Dose
0.58 m^2 to 0.83 m^2	NVP 200 mg (two 100-mg tablets)
0.84 m^2 to 1.16 m^2	NVP 300 mg (three 100-mg tablets)
≥1.17 m^2	NVP 400 mg (one 400-mg tablet)

Adolescent and Adult Dose:

- NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.[a,b]

Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed in patients who are also receiving NVP (see the Lopinavir/Ritonavir section for more information).

Metabolism/Elimination

- NVP is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a nevirapine dose is eliminated in urine as uridine diphosphate glucuronosyltransferase (UGT)-derived glucuronidated metabolites.

Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

- An additional dose of NVP should be given following each dialysis session.

Nevirapine Dosing in Patients with Hepatic Impairment:

- NVP should not be administered to patients with moderate or severe hepatic impairment.

[a] NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP induces CYP metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the immediate-release tablet formulation once daily instead of twice daily for the first 14 days of therapy. If there are no rashes or other AEs after 14 days of therapy, increase the dose of NVP to the age-appropriate full dose of the immediate-release tablet formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is NVP 200 mg per m^2 of body surface area once daily for the first 14 days, followed by NVP 200 mg per m^2 of body surface area twice daily thereafter. However, in children aged ≤2 years, some experts initiate NVP without lead-in dosing (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants below). In patients who are already receiving the full, twice-daily dose of the immediate-release tablets, extended-release tablets can be used without the lead-in period. Patients must swallow extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of NVP at the same time.** The dose should not exceed NVP 400 mg daily.

[b] Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have occurred in patients who were taking NVP. These toxicities are less common in children than adults. The majority of cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Nevirapine (NVP) induces hepatic cytochrome P450 (CYP), including 3A and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, leading to a 1.5-fold to two-fold increase in NVP clearance. There is potential for multiple drug interactions with NVP. Some genetic polymorphisms of CYP2B6 are associated with increased NVP serum concentrations. CYP2B6 polymorphisms vary among populations and may contribute to differences in NVP exposure. Please see the Efavirenz section for more information on how polymorphisms can alter enzyme activity.
- NVP should not be coadministered to patients who are receiving atazanavir (ATV) (with or without ritonavir), because NVP substantially decreases ATV exposure.
- NVP increases the metabolism of lopinavir (LPV). A dose adjustment of LPV is recommended when the two drugs are coadministered (see the Lopinavir/Ritonavir section).
- Before NVP is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

The following toxicities are seen with continuous dosing regimens, not during single-dose NVP prophylaxis.

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and elevated hepatic transaminases. NVP should be **discontinued and not restarted** in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated levels of hepatic transaminases. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing NVP resistance with extended lead-in dosing is unknown, and this concern must be weighed against the current antiviral response and a patient's overall ability to tolerate the regimen.
- *Less common (more severe):* Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. These toxicities are less common in children than adults. The majority of cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). Risk factors for NVP-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Children with CD4 percentages >15% have a three-fold increase in the risk of rash and hepatotoxicity after initiating NVP.[1] HSRs have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.
- *Less common (more severe):* In a cross-sectional study of 201 children with HIV aged 6 to 16 years, 43% of whom had hypertension, the use of NVP was associated with left ventricular hypertrophy (LVH) (adjusted odds ratio 3.14; confidence interval, 1.13–8.72; $P = 0.03$) but not left ventricular diastolic dysfunction.[2] The median duration on antiretroviral therapy (ART) in this cohort was 4.7 years (interquartile range 2.6–6.4 years). The majority of participants (76.6%) were receiving a regimen that included two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, the use of NVP was not associated with LVH in a more recent study by the same authors. LVH has been associated with NVP use in adults.[3,4]

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

NVP is approved by the Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of therapy, especially in resource-limited settings.[5-13] The extended-release tablet formulation has been approved by the FDA for use in children aged ≥6 years.

Efficacy in Clinical Trials

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to NVP in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over NVP in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics showed no differences in virologic outcomes between an NNRTI-based regimen (with either NVP or efavirenz [EFV]) and a protease inhibitor (PI)-based regimen in older children with HIV.[14-20]

In infants and children who were previously exposed to a single dose of NVP to prevent perinatal HIV transmission, NVP-based ART is less likely to control viral load than LPV/r-based ART. In P1060, 153 children with HIV and previous exposure to NVP for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine (ZDV) and lamivudine (3TC) plus either NVP or LPV/r. At 24 weeks post-randomization, 24% of children in the NVP arm had experienced virologic failure compared to 7% of children in the LPV/r arm ($P = 0.0009$); virologic failure was defined as <1 $\log_{10}$ decrease in HIV RNA during Weeks 12 to 24 or HIV RNA >400 copies/mL at Week 24. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the NVP arm met a primary endpoint compared to 22% of children in the LPV/r arm ($P = 0.027$).[17] Similar results were reported in a randomized trial that compared NVP and LPV/r in children aged 6 to 36 months who had not been previously exposed to NVP. This finding suggests that LPV/r-based therapy is superior to NVP-based therapy for infants, regardless of past NVP exposure.[14]

Extended-release NVP tablets (400 mg) were approved by the FDA for use in children aged ≥6 years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized, crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release NVP tablets and had plasma HIV RNA <50 copies/mL prior to enrollment. Participants were stratified according to age (3 years to <6 years, 6 years to <12 years, and 12 years to <18 years). Participants received immediate-release NVP tablets for 11 weeks. Participants were then treated with NVP extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PKs) were determined.[21] Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of extended-release NVP tablets through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with extended-release tablets, all 39 participants continued to have plasma HIV RNA <50 copies/mL.[22]

General Dosing Considerations

Body surface area has traditionally been used to guide NVP dosing in infants and young children. It is important to avoid underdosing NVP, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both NVP and EFV. Younger children (those aged ≤8 years) have higher apparent oral clearance than older children. In order to achieve drug exposures that are equivalent to those seen in children aged >8 years, younger children require higher doses of NVP than older children.[10,11] Because of this, it is recommended that children aged <8 years receive NVP 200 mg per m^2 of body surface area per dose twice daily (the maximum dose of the immediate-release tablet formulation is NVP 200 mg twice daily) or NVP 400 mg per m^2 of body surface area administered once daily as the extended-release tablet formulation (the maximum dose of the extended-release tablet formulation is NVP 400 mg once daily). For children aged ≥8 years, the recommended dose of the immediate-release tablet formulation is NVP 120 mg per m^2 of body surface area per dose (with a maximum dose of NVP 200 mg) administered twice daily. The maximum dose of the extended-release tablet formulation is NVP 400 mg once daily for children aged ≥6 years.

When adjusting the dose for a growing child, the milligram dose need not be decreased (from NVP 200 mg to NVP 120 mg per m^2 of body surface area) as the child reaches 8 years of age; rather, the milligram dose can be left static if there are no adverse effects, and the dose achieves the appropriate mg per m^2 of body surface area dose as the child grows. Some practitioners dose NVP at 150 mg per m^2 of body surface area every 12 hours or NVP 300 mg per m^2 of body surface area once daily if using the extended-release tablets regardless of age, as recommended in the FDA-approved product label. Regardless of age, the maximum dose should never exceed NVP 200 mg twice daily for immediate-release formulations of NVP or NVP 400 mg once daily for extended-release formulations of NVP.

Dosing Considerations: Lead-In Requirement

Underdosing during the lead-in period may have potentially contributed to the poorer performance of NVP in the P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to re-evaluation of lead-in dosing in children who have never received NVP. Traditionally, NVP is initiated with an age-appropriate dose that is given only once daily instead of twice daily (NVP 200 mg per m^2 of body surface area in infants aged ≥15 days and children aged <8 years, using the immediate-release formulations) during the first 2 weeks of treatment to allow for the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in NVP metabolism.

Studies have previously indicated that there is a potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.[23] The CHAPAS-1 trial[24] randomized 211 children to initiate ART with immediate-release NVP without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose once daily) for 2 weeks, followed by standard twice-daily dosing of the immediate-release formulation of NVP. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and there was no difference in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated NVP without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but the majority of participants were able to continue NVP therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 count and virologic failure endpoints.

After children had been on NVP for 2 weeks, investigators conducted a substudy that examined NVP plasma concentrations 3 to 4 hours after a morning dose of NVP. Among children aged <2 years, three of 23 children (13%) who initiated at full dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks compared to seven of 22 children (32%) who initiated at half dose ($P = 0.16$). There were no rash events in the substudy group of participants aged <2 years; in the parent CHAPAS study, there was a strong age effect on rash occurrence, with the risk of rash increasing with age. These findings suggest that a lead-in dose may not be necessary in young patients.[25]

Gopalan et al. analyzed NVP concentrations in 20 children who had a median age of 9 years and who were just starting an NVP-based ARV regimen. Subtherapeutic NVP concentrations, which were defined as trough concentrations ≤4 mcg/mL, occurred more frequently among children aged ≤8 years (n = 8) than among children aged >8 years (n = 12). Half of the children aged ≤8 years experienced virologic failure by Week 48.[26] The authors of the study suggested that rapid metabolism of NVP by CYP2B6 in this particular population may have confounded the results. The small number of participants in this study make the findings difficult to interpret, but the authors recommended a thorough review of NVP dose escalation strategies in children. Reinitiating half-dose NVP for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of NVP resistance, the half-life of the CYP enzymes,[27] and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends restarting full-dose NVP in children who interrupt therapy for 14 days or less.

Special Considerations for Dosing: Neonates and Premature Infants

For neonates and premature infants (which includes infants with corrected gestational ages of up to 42 weeks), PK data are currently inadequate to formulate an effective ARV regimen. Although dosing is available for ZDV and 3TC, data are inadequate for determining the appropriate doses for other ARV drugs. On the basis of PK

modeling, an investigational dose of NVP 6 mg/kg administered twice daily has been proposed for full-term infants who receive HIV diagnoses in the first few days of life.[28-32] However, a dose of NVP 4 mg/kg per dose twice daily has been chosen for the first week of life in infants born between 34 and 37 weeks' gestation, followed by NVP 6 mg/kg per dose administered twice daily thereafter. Dose adjustments may be required if a premature infant is found to have HIV during the first week of life. The PKs of NVP in patients who receive the investigational dose will be evaluated as part of IMPAACT 1115. Initial results from this study indicate that the experimental dosing schedule is safe and provides adequate PKs to maintain trough concentrations of NVP >3 mcg/mL in the majority of infants.[33] Providers who are considering initiating treatment in infants aged <2 weeks or in premature infants should contact a pediatric HIV expert for guidance, because the decision about whether to treat an infant and what drugs to use will involve weighing the risks and benefits of using unapproved ART dosing and incorporating case-specific factors, such as exposure to ARV prophylaxis.

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